Myelodysplastic Neoplasms

Update and diagnostic approach

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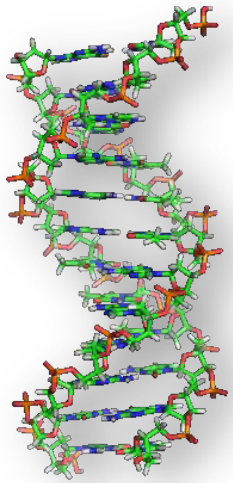
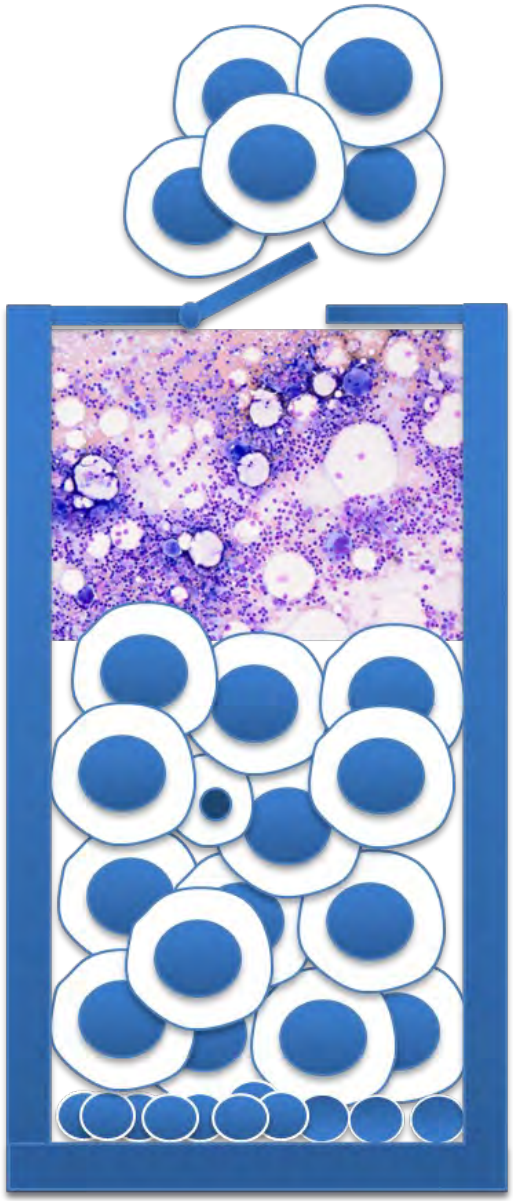


University of Nebraska Medical Center

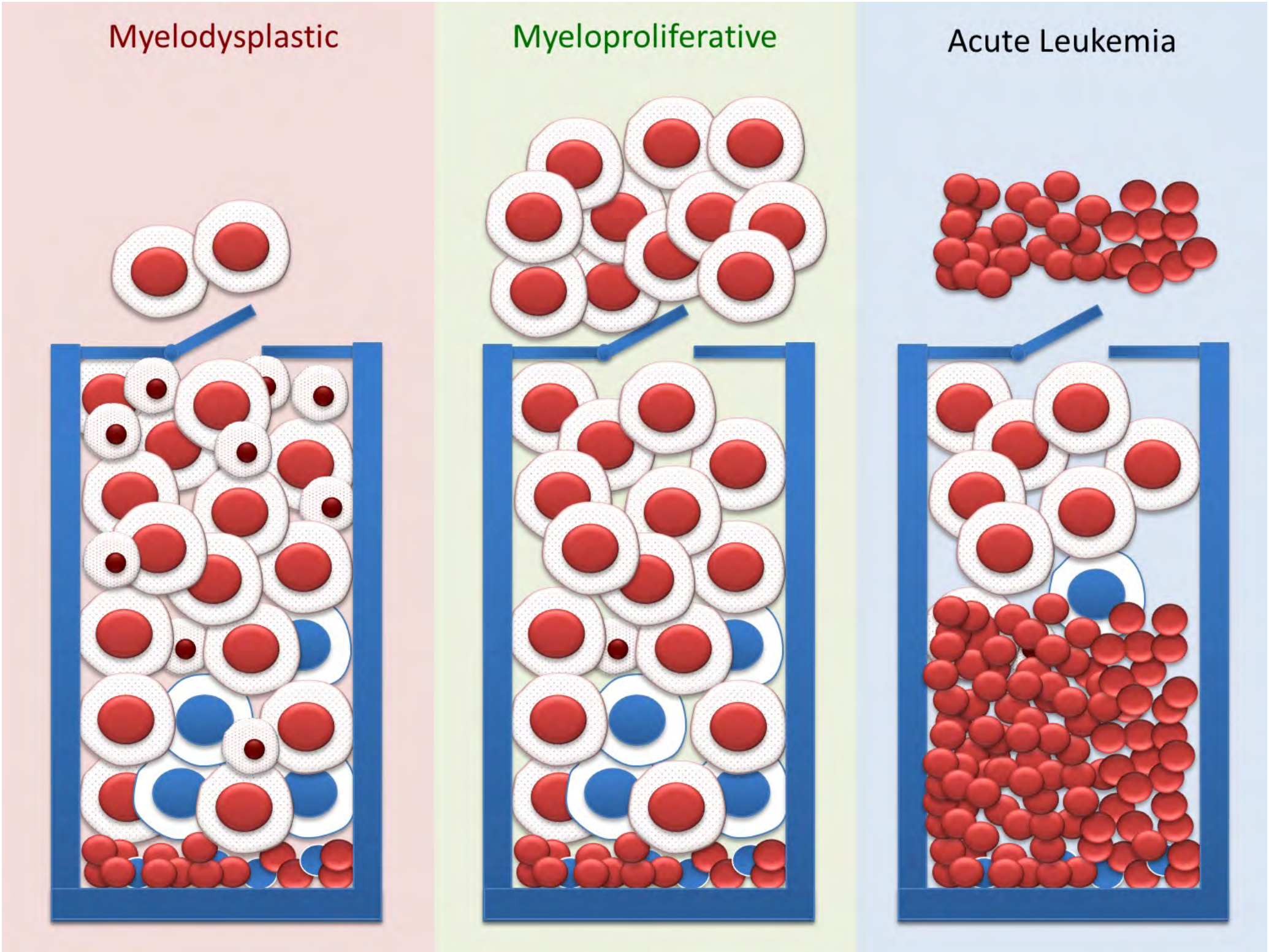
Nebraska Medicine

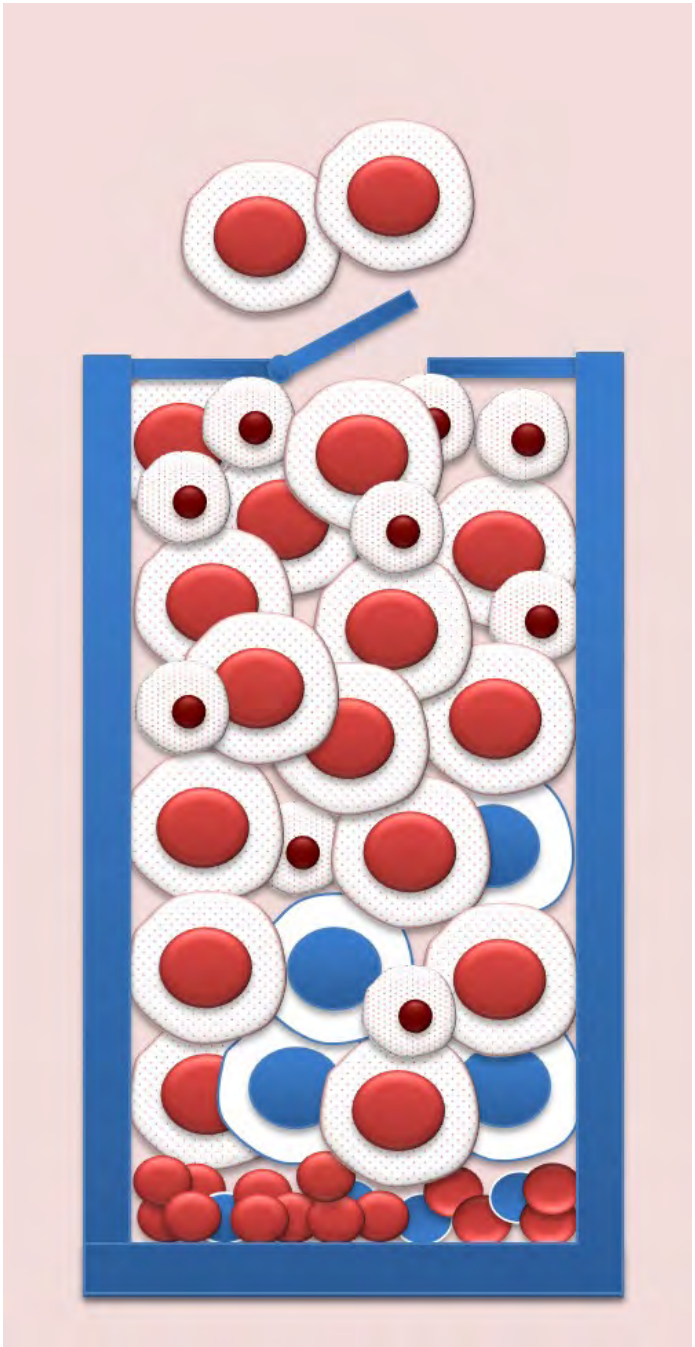
Apoptosis



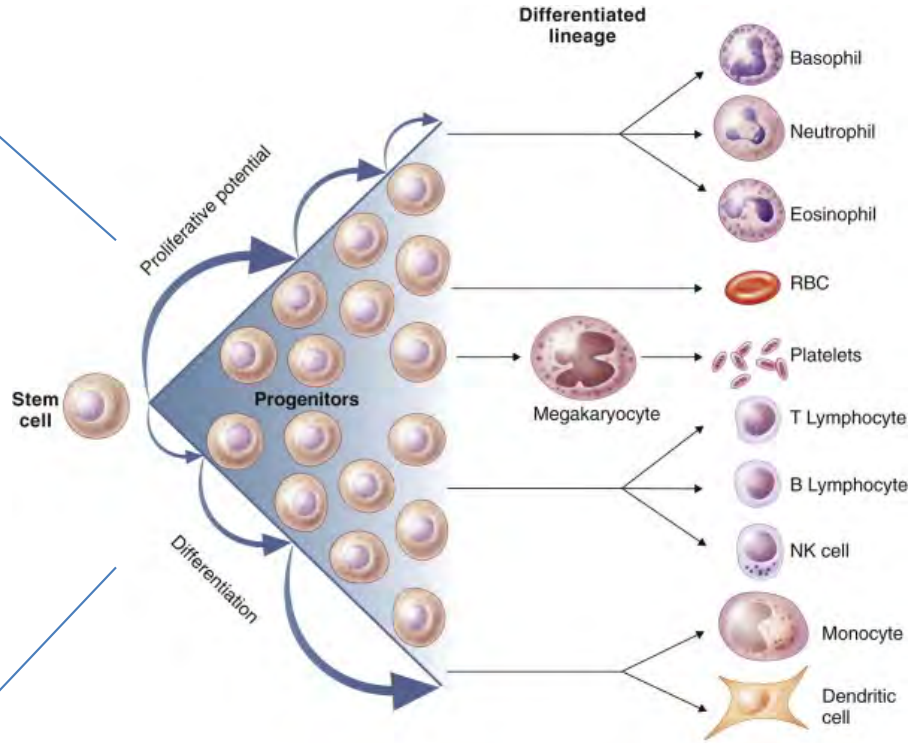
Proliferation

Differentiation


Myelodysplastic
Myeloproliferative
Acute Leukemia



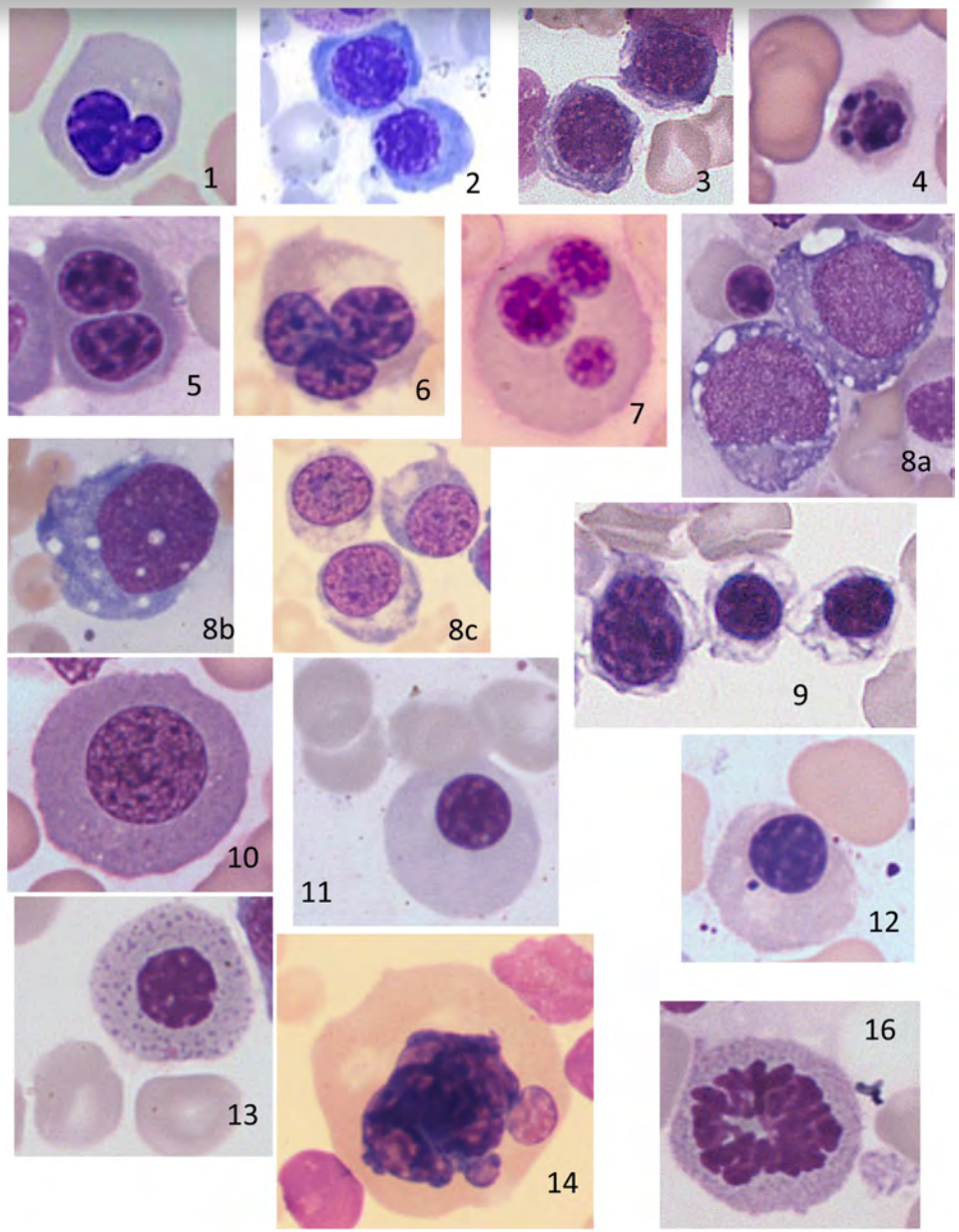
Myelodysplastic neoplasms are clonal hematopoietic stem cell neoplasms, defined by **cytopenias** *and* **morphologic dysplasia**, characterized by progressively ineffective hematopoiesis and increased risk of AML.



- **Anemia**
- **Thrombocytopenia**
- **Neutropenia**

Dyserythropoiesis

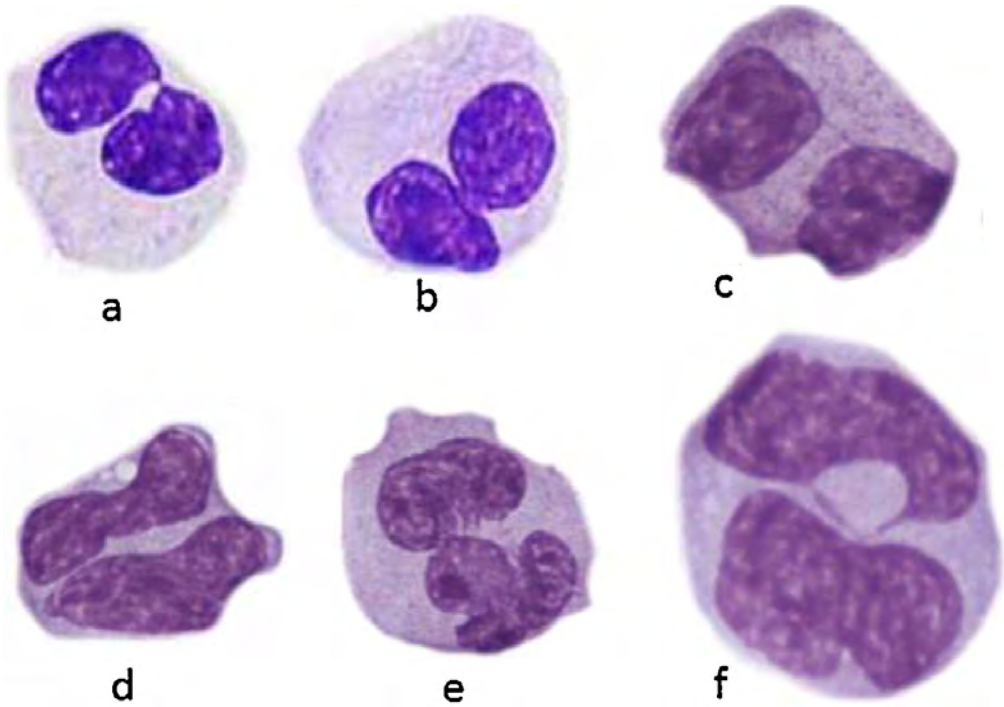
- Nuclear budding
- Internuclear bridging
- Karyorrhexis
- Multinuclearity
- Megaloblastoid changes
- Ring sideroblasts
- Cytoplasmic vacuoles



Goasguen JE *et al.* Br J Haematol 2018 Aug;182(4):526-533

Dysgranulopoiesis

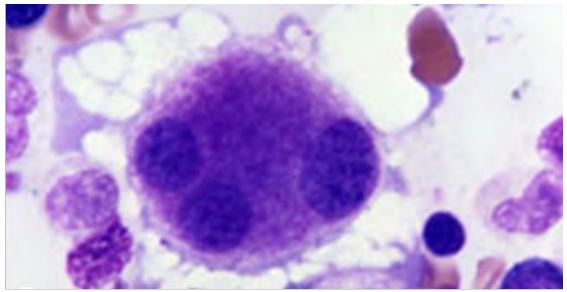
- Hypogranularity
- Nuclear hypolobation
- Small or large size
- Irregular hypersegmentation

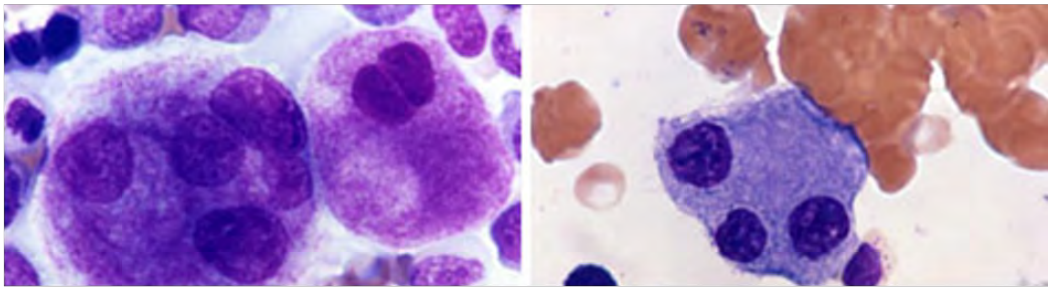


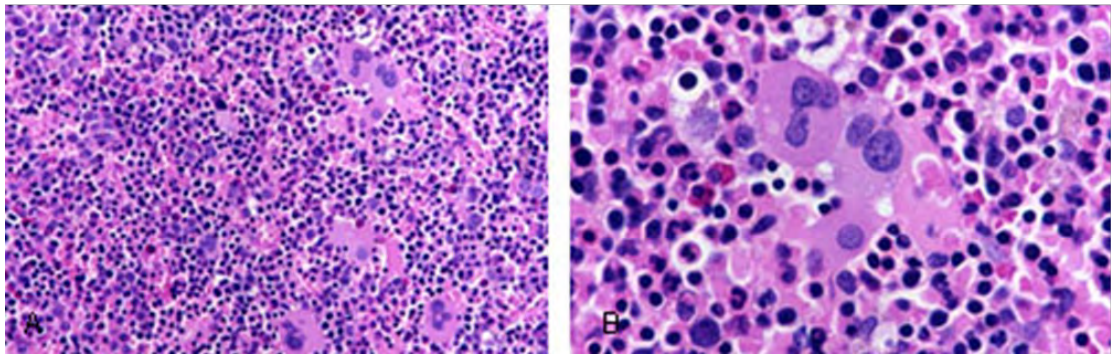
Goasguen JE *et al.* Leuk Res. 2014 Apr;38(4):447-53

Dysmegakaryopoiesis

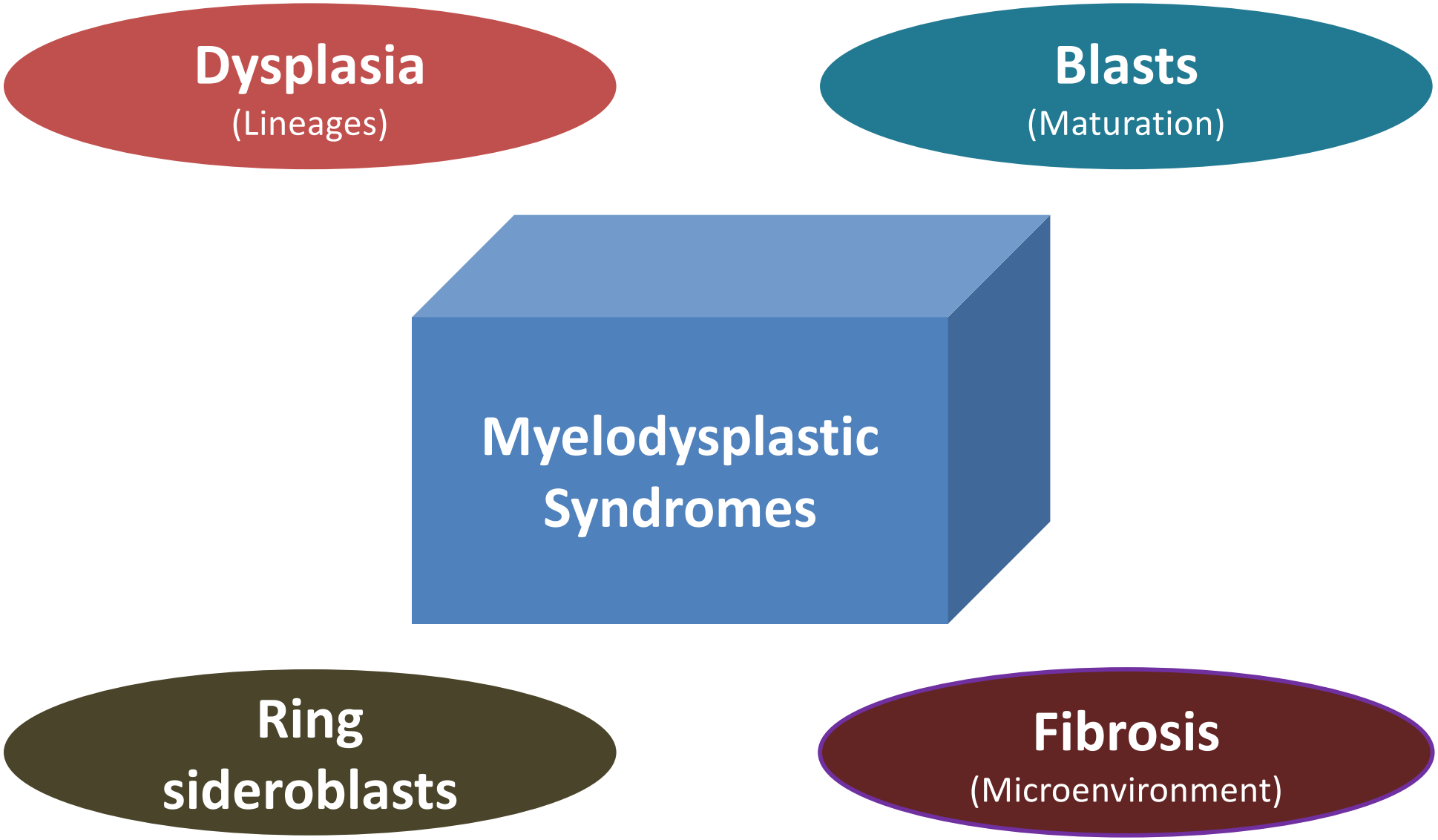
- Micromegakaryocytes
- Nuclear hypolobation
- Multinucleation



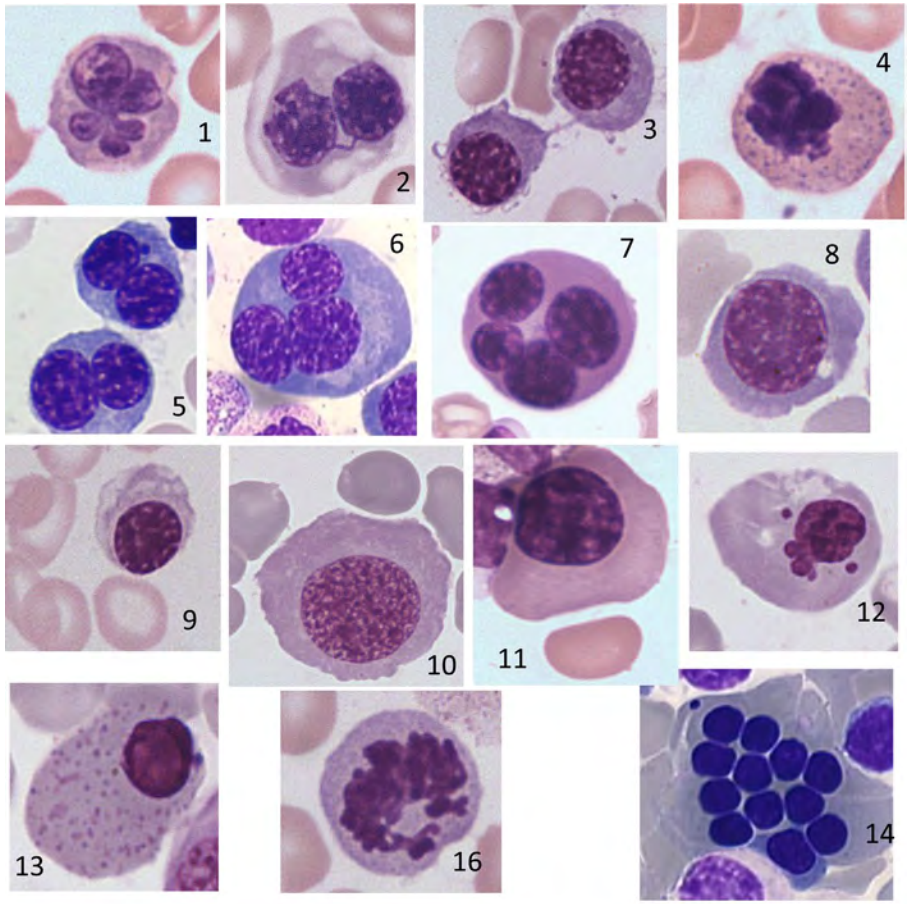


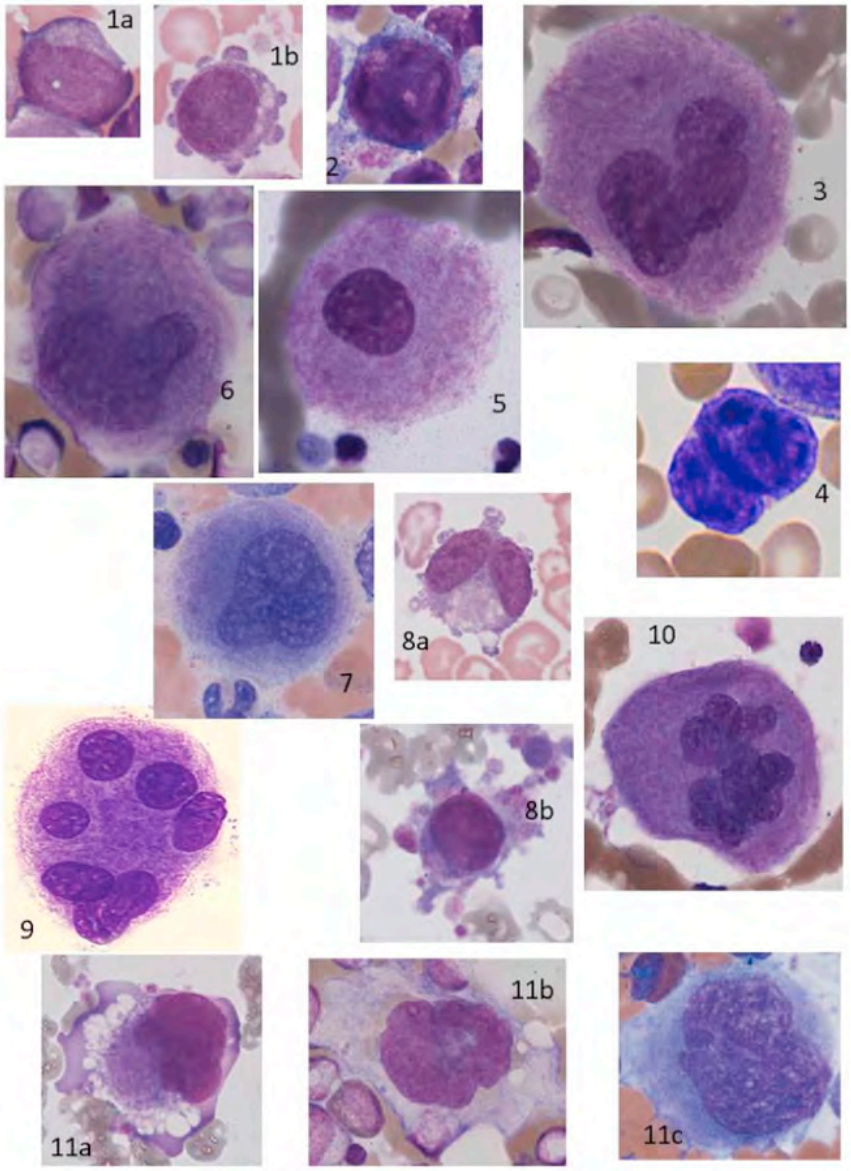


MORPHOLOGIC HALLMARKS



Mimics of morphologic dysplasia





Arsenic toxicity
Congenital dyserythropoietic anaemia (CDA)
Normal erythropoiesis
Copper deficiency
Iron deficiency
Vitamin B_{12} deficiency

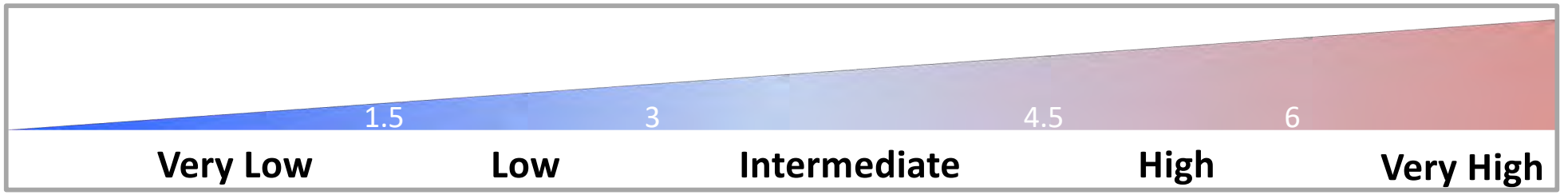
Goasguen JE *et al.* Br J Haematol 2018 Aug;182(4):526-533

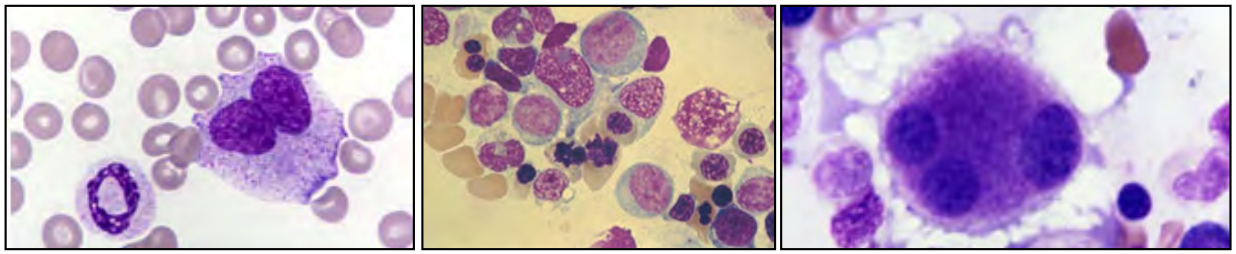
Goasguen JE *et al.* Leuk Res 2016 Jun;45:75-81.

Myelodysplastic Syndrome

Revised International Prognostic Scoring System (IPSS-R)

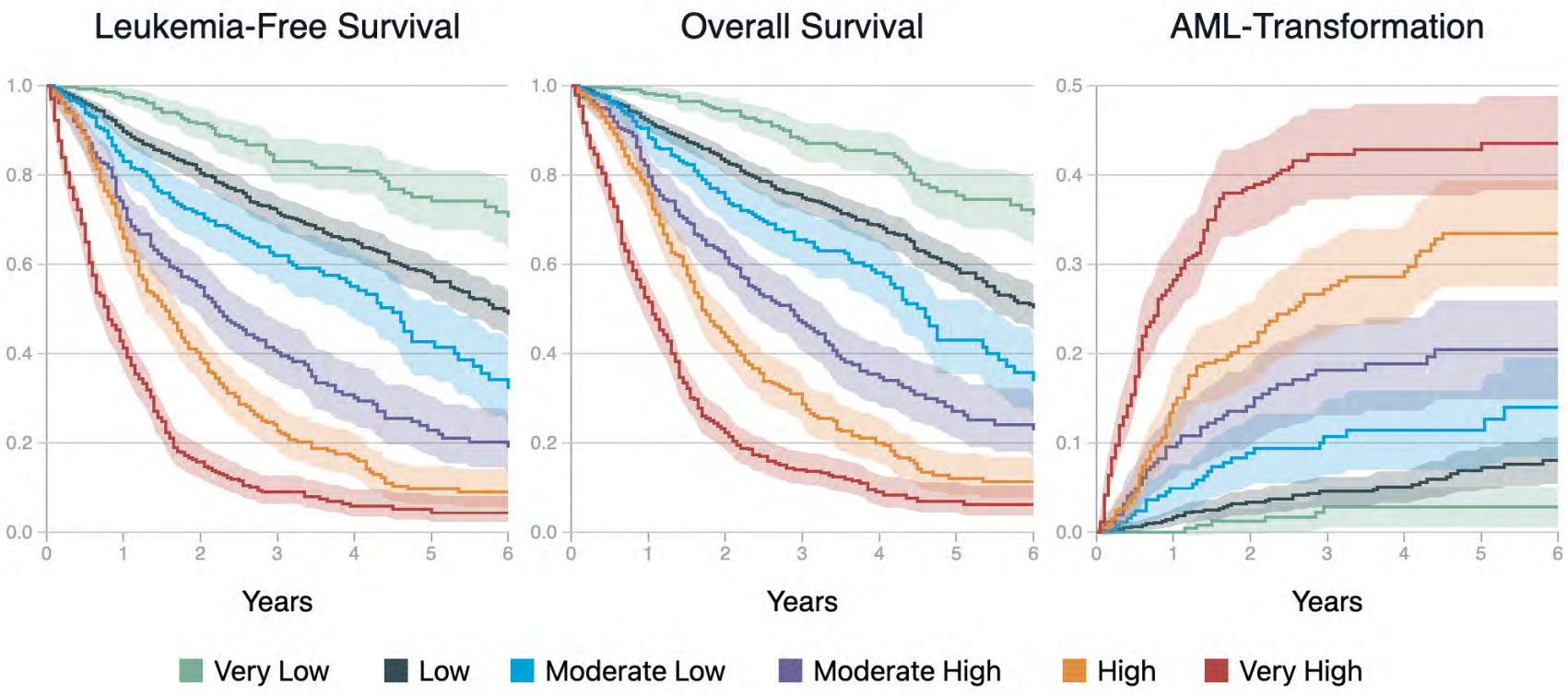
	0	0.5	1	1.5	2	3	4
Hemoglobin	≥10		8 - <10	<8			
Platelets	≥100	50 - <100	<50				
ANC	≥0.8	<0.8					
BM Blast %	≤2		>2 - <5		5-10	>10	
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor





Molecular International Prognostic Scoring System

Bone marrow blasts, hemoglobin, platelets, cytogenetics, mutations



Bernard et al. NEJM Evidence 2022 [mds-risk-model.com]

Benign **MDS**

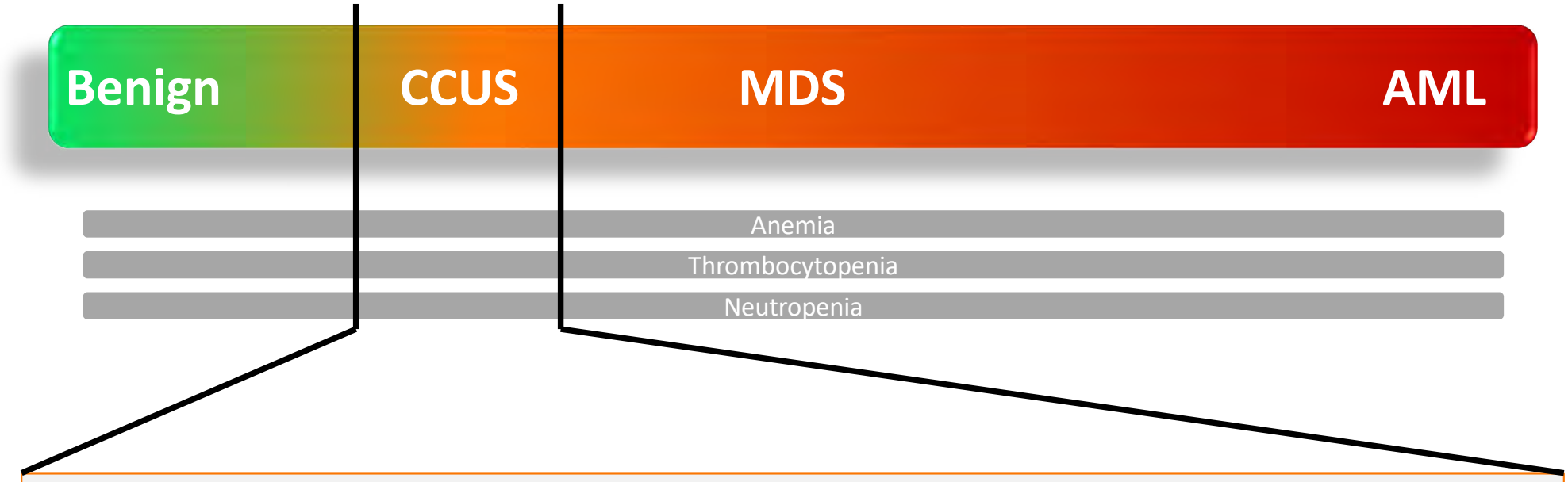
Anemia

Thrombocytopenia

Neutropenia

- Nutritional deficiencies
  - Iron
  - Vitamin B12
  - Folic acid
  - Copper
- Drug effect
- Infections
- Autoimmune diseases
- Toxin exposure
- Aplastic anemia
- Metabolic disorders

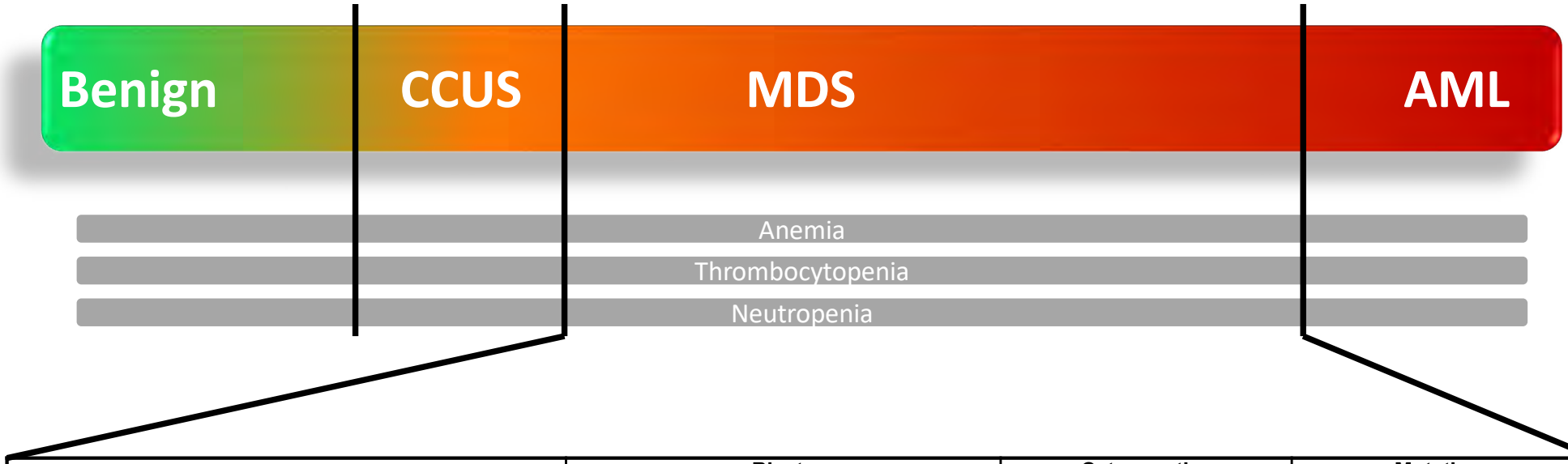
World Health Organization



- Definition as CHIP detected in the presence of ≥1 persistent unexplained cytopenias that do not meet diagnostic criteria for defined myeloid neoplasms.

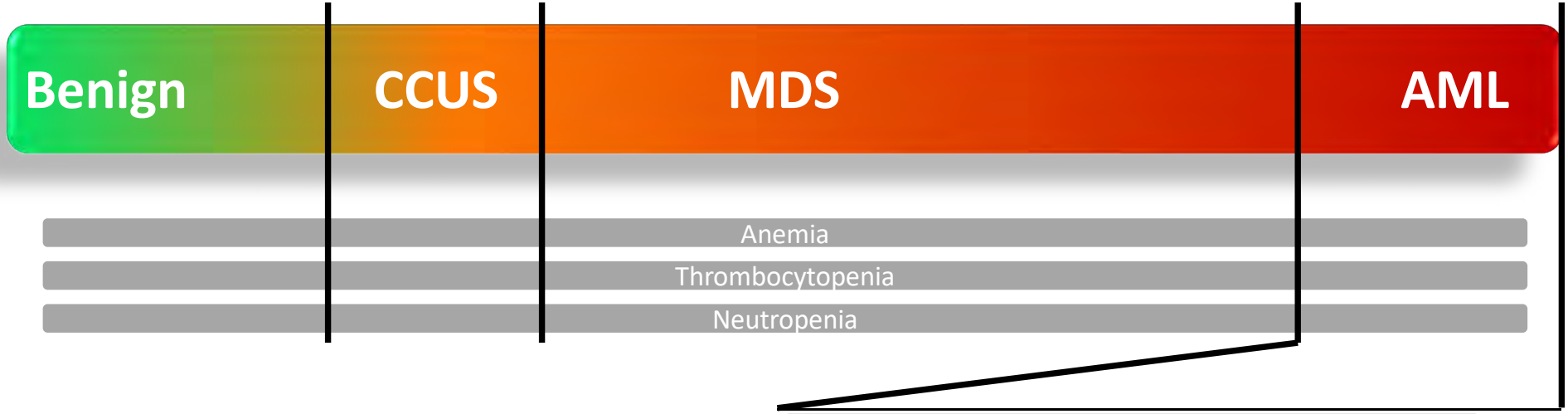
- Harmonized cytopenia definitions for CCUS, MDS, and MDS/MPN:
  - Anemia: Hb <13 g/dL males and <12 g/dL in females
  - Neutropenia: Absolute neutrophil count $<1.8 \times 10^9$/L
  - Thrombocytopenia: Platelets $<150 \times 10^9$/L

World Health Organization



	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and *SF3B1* mutation* (MDS-*SF3B1*)		Absence of 5q deletion, monosomy 7, or complex karyotype	*SF3B1*
MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB	Usually complex	Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic† (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5-9% BM or 2-4% PB		
MDS-IB2	10-19% BM or 5-19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5-19% BM; 2-19% PB		

World Health Organization

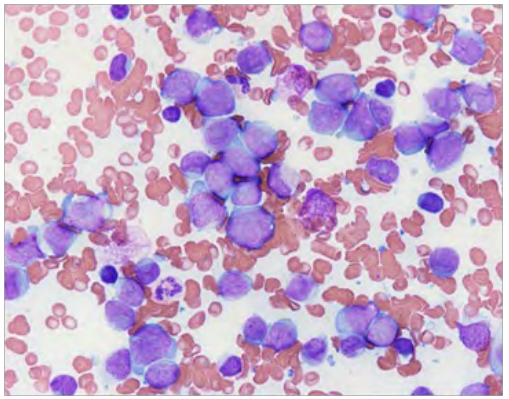


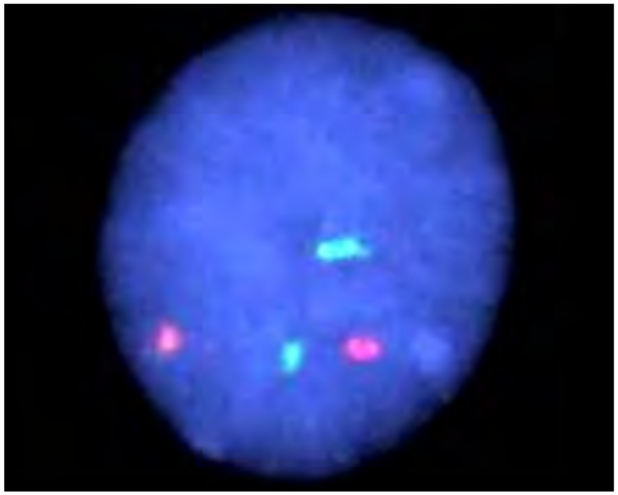
Acute myeloid leukaemia with defining genetic abnormalities

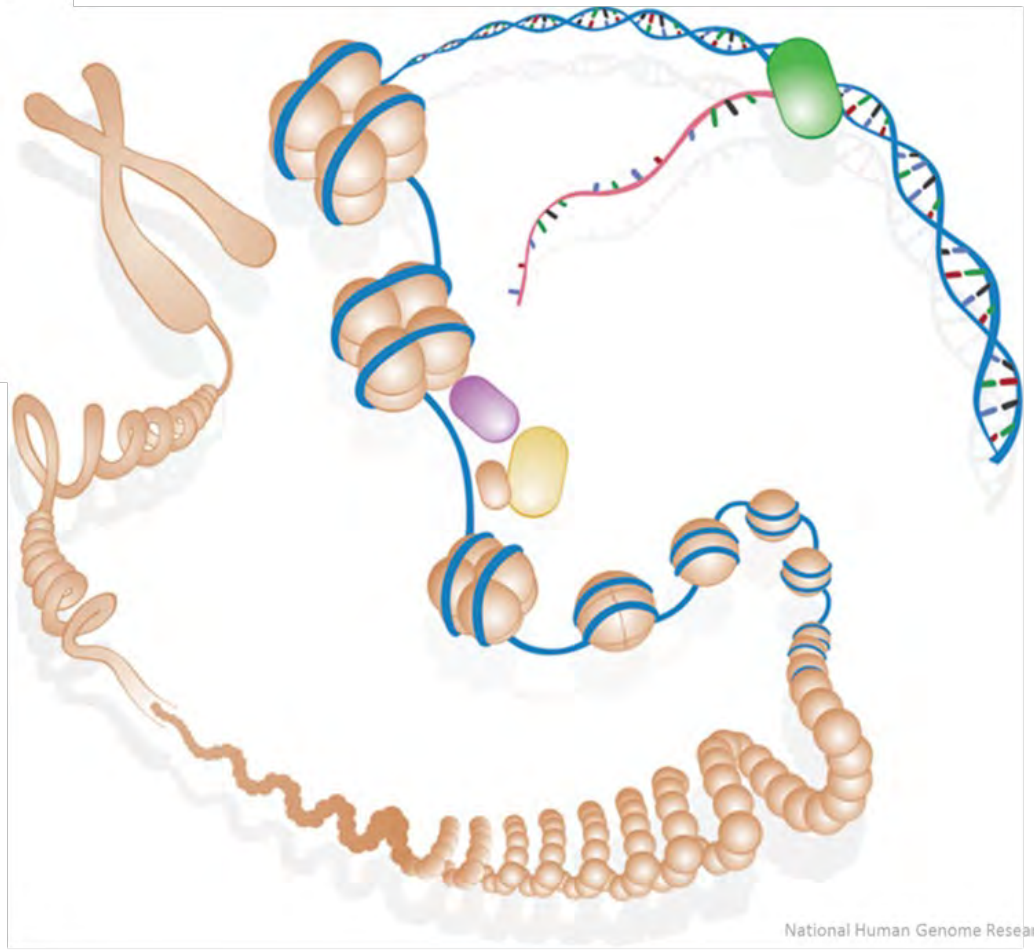
- Acute promyelocytic leukaemia with *PML*::*RARA* fusion
- Acute myeloid leukaemia with *RUNX1*::*RUNX1T1* fusion
- Acute myeloid leukaemia with *CBFB*::*MYH11* fusion
- Acute myeloid leukaemia with *DEK*::*NUP214* fusion
- Acute myeloid leukaemia with *RBM15*::*MRTFA* fusion
- Acute myeloid leukaemia with *BCR*::*ABL1* fusion
- Acute myeloid leukaemia with *KMT2A* rearrangement
- Acute myeloid leukaemia with *MECOM* rearrangement
- Acute myeloid leukaemia with *NUP98* rearrangement
- Acute myeloid leukaemia with *NPM1* mutation
- Acute myeloid leukaemia with *CEBPA* mutation
- Acute myeloid leukaemia, myelodysplasia-related
- Acute myeloid leukaemia with other defined genetic alterations

Acute myeloid leukaemia, defined by differentiation

- Acute myeloid leukaemia with minimal differentiation
- Acute myeloid leukaemia without maturation
- Acute myeloid leukaemia with maturation
- Acute basophilic leukaemia
- Acute myelomonocytic leukaemia
- Acute monocytic leukaemia
- Acute erythroid leukaemia
- Acute megakaryoblastic leukaemia

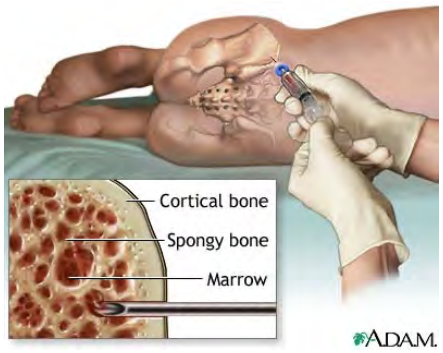






National Human Genome Research Institute

Hx, CBC, labs, order sets, etc.



Morphology → Hours / Days

Flow Cytometry → Hours

Cytogenetics → Hours / Days

Molecular Studies → Days

INTEGRATED REPORT

- **Aspirate smears**
  Touch preparations
  Clot preparation
  Trephine biopsy
- **Baseline**
  Follow up
- **Karyotype**
  FISH
- **DNA-based**
  RNA-based
  Panel
  Single

Mutation Profiling of Myeloid Neoplasms

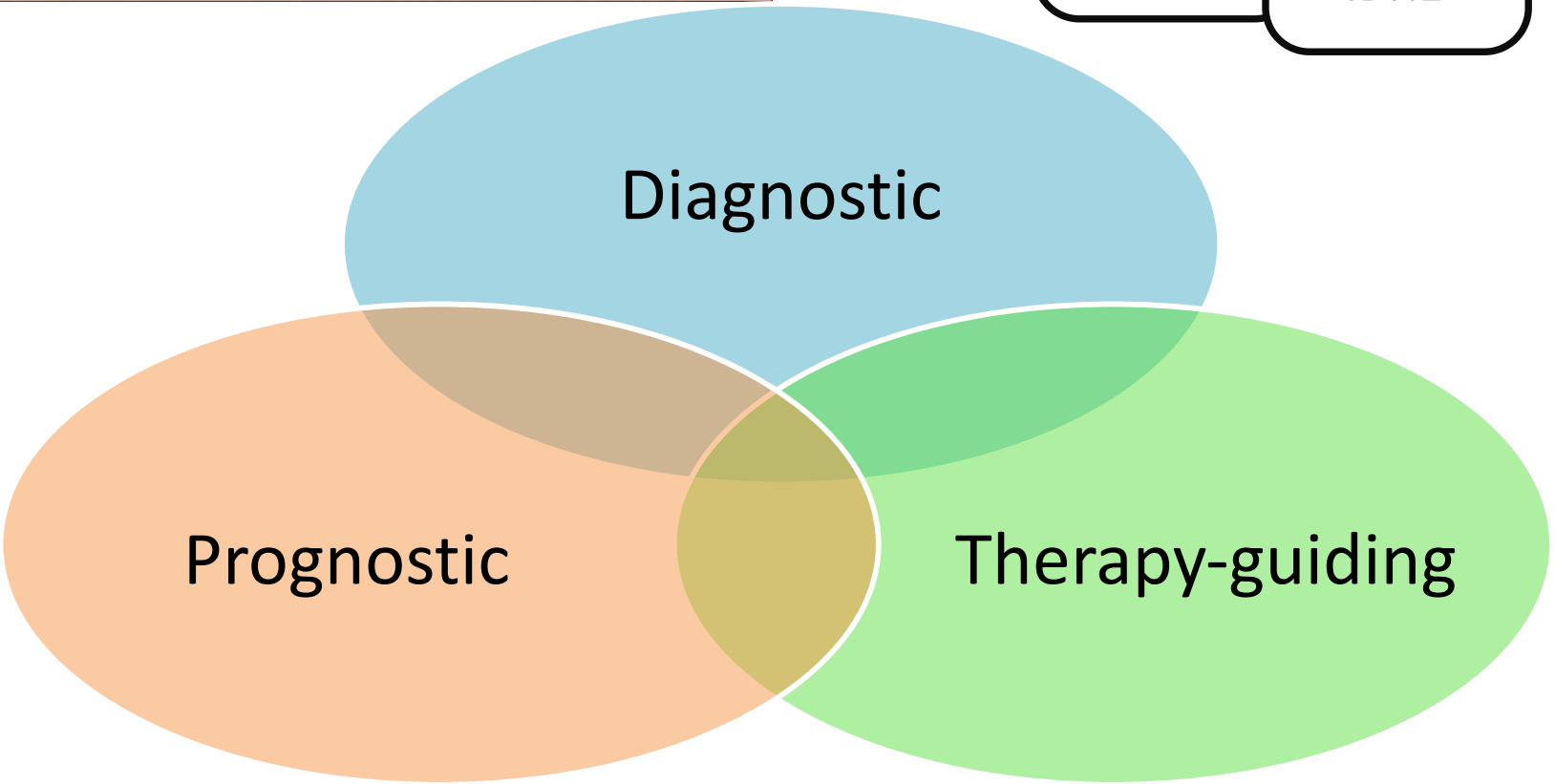
Molecular Diagnostics

ANKRD26	CBLB	EED	GFI1	JAK1	**NF1**	PTEN	SH2B3	SUZ12
ASXL1	CBLC	ELANE	GNAS	JAK2	NOTCH1	PTPN11	SMC1A	TERC
ASXL2	CEBPA	ETNK1	HNRNPK	JAK3	NPM1	RAD21	SMC3	TERT
BCOR	CREBBP	ETV6	HRAS	KDM6A	NRAS	RARA	SRSF2	TET2
BCORL1	CRLF2	EZH2	IDH1	KIT	PAX5	RUNX1	STAG1	TP53
BRAF	CSF3R	FBXW7	IDH2	KMT2A	PHF6	SETBP1	STAG2	U2AF1
BRINP3	CUX1	FLT3	IKZF1	KRAS	PIGA	SF1	STAT3	U2AF2
CALR	DDX41	GATA1	**IL2RG**	MAP2K1	PML	SF3A1	STAT5A	WT1
CBL	DNMT3A	GATA2	IL7R	MPL	PRPF40B	SF3B1	STAT5B	ZRSR2

TET2
ASXL1
CALR
CSF3R

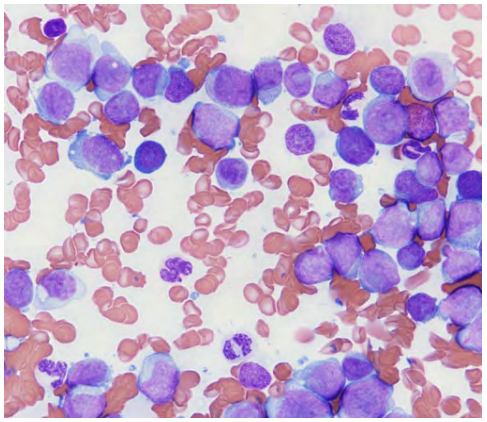
NPM1
TP53
RUNX1

JAK2
FLT3
KIT
IDH1
IDH2



Morphology

APL/CBF
Cytochemistry
Myelodysplasia
Ring Sideroblasts



Molecular

NPM1
FLT3-ITD
TP53, RUNX1
Rx Target

Flow Cytometry

Lineage
Rx Targets
MRD

Cytogenetics

Diploid
Complex
MDS-related

Antecedent HM
Cytotoxic Rx
Family history

Microenvironment

Clinical

Fibrosis
Immune deregulation

Thank you!